REMARKS

Claims 23-40 were pending in the instant application. Claims 23 and 33-35 have been amended. Claims 23 and 35 have been amended to correct a formality. Support for the amendment to claims 33 and 34 can be found in the specification at least at page 42, lines 1-4. No new matter has been added.

Applicants request that the amendments to the specification and claims be entered. Amendment of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to more particularly point out and distinctly claim Applicants' invention in order to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Applicants would like to thank the Examiner for participating in an interview with Applicants' attorney on June 9, 2003 regarding the pending claims and the enablement rejection.

Rejection of Claims 23-32 Under 35 U.S.C. §101

Applicants gratefully acknowledge the Examiner's withdrawal of the rejection under 35 U.S.C. § 101.

Rejection of Claims 23-40 Under 35 U.S.C. §112, First Paragraph

Claims 23-40 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The Examiner states that while the specification is enabling with regard to a transgenic mouse, the specification "does not reasonably provide enablement for all other transgenic organisms embraced by the claims." Applicants respectfully traverse this rejection.

Claim 23 is directed to a transgenic non-human animal having a transgene integrated into the genome of the non-human animal and also having a *tet* operator-linked

gene in the genome of the organism-human animal. The transgene of claim 23 comprises a transcriptional regulatory element functional in cells of the non-human animal operatively linked to a polynucleotide sequence encoding a fusion protein which activates transcription of said *tet* operator linked gene, wherein the fusion protein comprises a first polypeptide which is a Tet repressor operatively linked to a second polypeptide which directly or indirectly activates transcription in eukaryotic cells. The *tet* operator-linked gene of claim 23 further confers a detectable and functional phenotype on the non-human animal when expressed in its cells, wherein the transgene is expressed in cells of the non-human animal at a level sufficient to produce amounts of the fusion protein that are sufficient to activate transcription of the *tet* operator-linked gene, and in the absence of tetracycline or a tetracycline analogue in the non-human animal, said fusion protein binds to the *tet* operator-linked gene and activates transcription of the *tet* operator linked gene such that the *tet* operator-linked gene is expressed at a level sufficient to confer the detectable and functional phenotype on the organism, wherein the level of expression of the *tet* operator-linked gene can be downmodulated by administering tetracycline or a tetracycline analogue to the non-human animal.

Claim 24 is directed to a transgenic non-human animal having a transgene integrated into the genome of the non-human animal, wherein the transgene comprises a transcriptional regulatory element functional in cells of the non-human animal operatively linked to a polynucleotide sequence encoding a fusion protein which activates transcription of a *tet* operator linked gene, the fusion protein comprising a first polypeptide which is a Tet repressor, operatively linked to a second polypeptide which directly or indirectly activates transcription in eukaryotic cells, and said fusion protein is expressed in cells of the non-human animal. In addition, claims 33 and 34, which depend from claims 23 and 24 respectively, are directed to non-human animals selected from the group consisting of a mouse, a cow, a sheep, a goat, and a pig.

Claim 35 is drawn to a transgenic non-human animal selected from the group consisting of a mouse, a cow, a sheep, a goat, and a pig, having a transgene integrated into the genome of the non-human animal and also having a *tet* operator-linked gene in the genome of the non-human animal, wherein the transgene comprises a transcriptional regulatory element functional in cells of the non-human animal operatively linked to a polynucleotide sequence encoding a fusion protein which activates transcription of said *tet* operator linked gene, the fusion protein comprises a first polypeptide which Tet repressor operatively linked to a second polypeptide which directly or indirectly activates transcription in eukaryotic cells, said *tet* operator-linked gene confers a detectable and functional phenotype on the organism when expressed in cells of the non-human animal, said transgene is expressed in cells of the non-human animal at a level sufficient to produce amounts of said fusion protein that are sufficient to activate transcription of the *tet* operator-linked gene, and in the absence of tetracycline or a tetracycline analogue in the non-human animal, said fusion protein binds to the *tet* operator-linked gene and activates transcription of the *tet* operator linked gene such that the *tet* operator-linked gene is expressed at a level sufficient to confer the detectable and functional phenotype on the organism, wherein the level of expression of the *tet* operator-linked gene can be downmodulated by administering tetracycline or a tetracycline analogue to the non-human animal.

Claim 36 is directed to a transgenic non-human animal selected from the group consisting of a mouse, a cow, a sheep, a goat, and a pig having a transgene integrated into the genome of the non-human animal, wherein the transgene comprises a transcriptional regulatory element functional in cells of the non-human animal operatively linked to a polynucleotide sequence encoding a fusion protein which activates transcription of a *tet* operator linked gene, the fusion protein comprising a first polypeptide which is a Tet repressor, operatively linked to a second polypeptide which directly or indirectly

activates transcription in eukaryotic cells, and said fusion protein is expressed in cells of the non-human animal.

The Examiner asserts that Applicants claim the tTA system transcribes the gene of interest alone (see page 4 of Office Action), however, Applicants clarify that the tTA system described in the instant invention is a highly regulated transcriptional system which works with endogenous transcriptional machinery to directly or indirectly activate transcription of a gene of interest operatively linked to a *tet* operator, based on the presence or absence of an effector molecule (tetracycline (Tc)) binding to a TetR activator fusion. Applicants did not mean to infer that transcription occurred only with the TetR-activator fusion. Applicants maintain that the *tet* regulatory system described in the transgenic non-human animals of the invention provides a reliable, predictable method of controlling gene expression, because the claimed system does not rely on endogenous transcriptional ***activators and/or inhibitors***, *i.e.*, proteins which enhance or inhibit transcriptional activity, which may or may not be present in the cell. Applicants invention includes transgenic non-human animals having a *tet* operator-linked transgene and a TetR fusion protein transgene, wherein transcriptional activation depends upon the TetR fusion protein whose activity is controlled by an exogenous effector molecule (tetracycline or a tetracycline analogue). Applicants provide a working example in the instant specification (see generation of transgenic tTA mice as described in Example 1, pages 51-52) which demonstrates that the resulting phenotype is the successful regulation of luciferase (the chosen gene of interest) under the control of the *tet* system.

The Examiner states that the claimed invention is not enabled because the specification does not teach one of ordinary skill in the art to make the claimed transgenic non-human animal, including cows, sheep, goats, and pigs, comprising a tTA system. The Examiner states that the previously cited references demonstrate the unpredictability in making a transgenic non-human animal, including a cow, sheep, goat, or pig.

comprising a tTA system, particularly with regard to the "unpredictability of a phenotype resulting from expression of a transgene in different species of non-human animals." Applicants respectfully traverse this rejection .

Applicants maintain that the methodologies taught in the instant specification regarding the production of transgenic animals, as well as the general knowledge (as exemplified by the references submitted in Applicants' response of April 1, 2003) in the art at the time of filing, fully support the claimed invention, specifically non-human transgenic animals other than mice.

In Applicants' response of April 1, 2003, a number of scientific publications were submitted in support of Applicants' position that transgenic animals comprising an exogenous gene had been successfully produced at the time of filing of the priority application, and that it was routine in the art at the time of filing to produce transgenic animals other than mice, including pigs, sheep, and goats. The previously submitted references include the following:

Pursel *et al.* (1990), who teach the production of transgenic pigs which express bovine and human growth hormone (previously submitted Appendix B);

Rexroad *et al.* (1991), who teach the production of transgenic sheep expressing bovine or human growth factor-releasing hormone (previously submitted Appendix C); and

Ebert *et al.* (1991), who teach the production of transgenic goats expressing a human tissue-type plasminogen activator (previously submitted as Appendix D).

In addition to those described above, Applicants provide the following references to further support that transgenic non-human animals other than mice had been created at the time of filing:

K and L. WO 92/22646 and WO 93/25017, entitled "Production of Human Hemoglobin Transgenic Pigs" (attached herewith as Appendix K and L, respectively;

hereinafter referred to as '646 and '071, respectively) teach the production of transgenic pigs expressing the human hemoglobin gene.

M. U.S. patent no. 5,366,894, entitled "Protein Production" (attached herewith as Appendix M; hereinafter referred to as '894) teaches a method of producing transgenic sheep who express a desired transgene in their milk, wherein the protein can be easily collected and purified.

N. Fodor *et al.* (1994) *PNAS* 91:11153-11157 (attached herewith as Appendix N; hereinafter referred to as "Fodor") who describe the production of transgenic pigs which express human CD59;

O. Kroshus *et al.* (1996) *Transplantation* 61:1513-1521 (attached herewith as Appendix O; hereinafter referred to as "Kroshus") who describe transgenic pigs who express human CD59 on their organs in order to decrease the chance of rejection in xenotransplantation. The Kroshus paper follows the experiment described in the above-mentioned Fodor publication, and demonstrates that the transgenic pigs originally described in Fodor were successfully used in subsequent studies;

P. Wall *et al.* (1996) *Transgenic Research* 5:67-72 (attached herewith as Appendix P; hereinafter referred to as "Wall") who describe transgenic sheep which express the whey acidic protein (WAP); and

Q. PCT publication no. WO 97/19589 (attached herewith as Appendix Q; hereinafter referred to as '589) teaches methods of producing transgenic goats, including how to obtain goat stem cells.

Applicants point out to the Examiner that it is common practice in the production of transgenic non-human animals to first examine the initial litter or group of potential transgenic animals in order to determine which of the first generation has the transgene integrated into the animal's genome. From this initial litter of animals, a population of transgenic organisms is identified and is referred to as the "founders," wherein each

animal potentially has a different genetic identity, *i.e.*, number of copies of the transgene, different integration sites, etc., from which the desired "founder" animal(s) will be selected. As described in the working example of the instant specification, as well as in the above-mentioned publications, founder transgenic animals often display different characteristics of the transgene depending on, for example, integration site within the genome, including the "position effect," number of copies of the transgene, etc. These differences are recognized by the ordinarily skilled artisan through known nucleic acid assays which examine the transgene properties, such as PCR (see instant specification, Example 1), Northern blot analysis (see Wall), and DNA slot blot analysis (see Fodor). As taught by Applicants in the working example, each of the founder transgenic animals can be analyzed to determine the transgene expression which correlates with the phenotype.

Identified "founder animals" are then selected for breeding, as taught by Applicants, in order to "breed additional animals carrying the transgene" and to produce transgenic animals displaying the desired phenotype and transgene expression (see page 11, lines 12-13 of instant specification). For example, in Kroshus, three founder piglets were identified where one piglet was found to have 10-20 copies of the transgene, while the other two piglets had only about one copy of the transgene and showed very little and inconsistent transgene expression. The founder piglet with 10-20 copies was used to produce a transgenic line of piglets, which had a predictable and consistent phenotype, *i.e.*, high level cell surface expression of hCD59. The founder piglet was subsequently used for further analysis of the transgenic pigs comprising the human hCD59 gene, as described in Kroshus. Thus, Applicants submit that while the initial litter of transgenic animals had different transgene and phenotypic characteristics, those with the desired characteristics can be chosen to act as founders in the production of a transgenic line of non-human animals with predictable and consistent phenotypes. Accordingly, the

specification meets the enablement requirement and Applicants thus respectfully request that the rejection of claims 23-34 under U.S.C. § 112 first paragraph, be withdrawn.

Rejection of Claims 23, 25, 27, 29, 30-31, 33, 35, 37, and 39 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 23, 25, 27, 29, 30-31, 33, 35, 37, and 39 Under 35 U.S.C. §112, second paragraph as being indefinite for reciting the phrase "the organism," which has no antecedent basis in the claims. The claims have been amended to correct for this recitation, thus rendering the rejection moot.

Rejection of Claims 23-40 Under the Judicially Created Doctrine of Obviousness-Type Double-Patenting

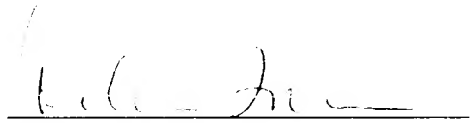
Claims 23-34 have been rejected under the judicially created doctrine of obviousness-type double patenting over U.S. Patent No. 5,859,310. Applicants will address this issue upon an indication of allowable subject matter.

CONCLUSION

In view of the foregoing remarks, reconsideration of the rejections and allowance of all pending claims is respectfully requested.

If a telephone conversation with Applicants' attorney would expedite the prosecution of the above-identified application, the examiner is urged to call Applicants' attorney at (617) 227-7400.

Respectfully submitted,
LAHIVE & COCKFIELD, LLP



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